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(21) International Application Number: PCT/GB87/00550 (22) International Filing Date: 3 August 1987 (03.08.87) (31) Priority Application Numbers: 8618949 8621448 (32) Priority Dates: 2 August 1986 (02.08.86) 5 September 1986 (05.09.86) (33) Priority Country: GB (71) Applicant (for all designated States except US): FISONS PLC [GB/GB]; Fison House, Princes Street, Ipswich IP1 1QH (GB). (72) Inventors; and (75) Inventors/Applicants (for US only) : ALSOP, Ranulph, Michael [GB/GB]; 28 Windemere Drive, Alderley Edge, Cheshire SK9 7UP (GB). FORRESTER, Raymond, Brian [GB/GB]; 7 Alderley Close, Sandbach, Cheshire (GB). GRIFFIN, George [GB/GB]; 8 Buxton Drive, New Malden KT3 3UZ (GB). MILNER, Jeremiah [IE/IE]; Milner Laboratories, Dungar House, Roscrac, Co. Tipperary (IE).		(74) Agent: WRIGHT, Robert, Gordon, McRae; Fisons plc, 12 Derby Road, Loughborough, Leicestershire LE11 0BB (GB). (81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US. Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: USE OF CERTAIN POLYSACCHARIDES FOR THE TREATMENT OF HEPATIC OR RENAL FAILURE (57) Abstract Method of treatment of a patient suffering from hepatic or renal failure which comprises administration of a dextran of Mw in the range 10,000 to 50,000,000, optionally in admixture with glucose polymers other than dextran, and in particular those containing an average of 2 - 10 glucose units per molecule.		

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Use of certain polysaccharides for the treatment of hepatic or renal failure.

Technical Field

This invention relates to novel compositions for, and
5 to the use of certain polysaccharides in, the treatment of conditions arising from hepatic or renal failure.

Nitrogenous waste products, such as ammonia, are usually converted in the liver to products that may be excreted, eg urea. Such products are then transported to
10 the kidneys where they are excreted from the body. Failure of either of the kidneys or liver to carry out such functions may lead to an increased concentration of waste products which are toxic to the body.

Hepatic and/or portosystemic encephalopathy may occur
15 where there is a high concentration of ammonia circulating in the blood stream. Ammonia is produced in the gut by the action of bacteria on ingested proteins and is absorbed into the portal blood stream from the large intestine. Patients suffering from hepatic failure or
20 portosystemic shunting can not adequately convert the ammonia to urea in the liver for excretion, so that excess ammonia may enter the systemic blood system.

Patients who have defective kidneys or who have had their kidneys removed tend to have a high metabolic rate.
25 This can lead to the metabolism of stored proteins, which

in turn increases the production of unwanted nitrogenous products in their bodies and consequently produces a further load on their defective kidneys or a build up of toxic metabolites in their serum.

5 Background Art

It is known to remove water and waste products from the body by means of peritoneal dialysis and haemodialysis.

Also there are known two methods for the treatment of hepatic and portosystemic encephalopathy. One is to
10 attack the ammonia producing bacteria, ie by administering an antibiotic such as neomycin. The other is to limit the absorption of ammonia in the large intestine, for example by administration of lactulose (4-O- β -D-Galactopyranosyl-D-fructose). Lactulose increases the rate of passage
15 through the gut, and also produces an acidic environment in the large intestine which allows ammonia to be converted to ammonium ions which are excreted from the body unabsorbed. However large doses of lactulose must be administered to obtain the desired effect.

20 Gastrointestinal disturbances such as nausea and flatulence may occur with such large doses. Also lactulose is a small molecule, a synthetic disaccharide, and its administration as a large dose may lead to loss of free water through osmotic diarrhoea which may in turn
25 lead to hypernatremia, a condition which can be fatal for

the patient.

It is also known that patients suffering from renal failure can be treated by the oral administration of a low molecular weight dextrin which provides a rapidly available source of energy as absorbed glucose. The presence of the glucose reduces the metabolism of the stored body protein and thereby reduces some of the load of nitrogenous products on the kidneys.

We have now found a means of mitigating some of the problems of patients who have defective livers or kidneys.

Disclosure of the Invention

According to the invention we provide a method of treatment of a patient suffering from hepatic or renal failure, which comprises administration of an effective amount of a dextran of weight average molecular weight in the range 10,000 to 50,000,000 to a patient suffering from such a condition.

The dextran preferably has a weight average molecular weight in the range 50,000 to 1,000,000, more preferably in the range 60,000 to 400,000.

By dextran we mean a polyglucose or a derivative thereof in which the glucose units or their derivatives are predominantly linked in an alpha 1,6 configuration. Specific derivatives include hydrogenated dextran, dextran glucoheptonic acid, carboxymethyl dextran and hydroxyethyl

dextran. Dextrans can be made by the action of the dextranucrase family of enzymes on sucrose.

Dextranucrases are produced by various species of lactobacillae. We particularly prefer dextrans produced
5 by Leuconostoc mesenteroides (and especially strain NRRL B512F). The dextrans produced by the action of the enzymes on sucrose are generally of very high molecular weight and may be partially hydrolysed and the hydrolysate fractionated, if desired, to produce fractions of
10 relatively narrow bands of lower molecular weight. We prefer to use these fractionated dextrans. These dextrans are generally available in commerce and are of the same general type as, but are usually of a higher molecular weight than, the dextrans which are currently
15 used for intravenous administration.

According to the invention we also provide a dextran of weight average molecular weight of from 10,000 to 50,000,000 for use in the manufacture of a medicament for the treatment of hepatic or renal failure.

20 The medicament may be in a form suitable for i.v., rectal or preferably oral administration.

For oral administration the medicament may be in the form of a syrup, a tablet, a dry powder, which may be dissolved in a suitable solvent, eg water prior to
25 administration, or a liquid, eg an aqueous solution. The

medicament may be incorporated into either a liquid or solid foodstuff, eg bread, biscuits, yoghurt, tea or coffee.

For rectal administration we prefer the medicament to be in the form of an enema and in particular to be an aqueous solution. We prefer the enema to contain up to 15% w/v, eg 7.5% w/v of the dextran.

For i.v. administration we prefer the medicament to contain up to 15% w/v, eg 6 - 10% w/v of the dextran.

10 The medicament may also contain a pharmaceutically acceptable adjuvant, diluent or carrier. For tablets suitable adjuvants, diluents and carriers are lactose, starch, talc or stearic acid and, for i.v. formulations or enemas, surfactants and preservatives. The i.v. formulations and enemas may be made isotonic with, for example, sodium chloride or phosphate.

The medicament may also contain other ingredients, such as flavours, eg fruit flavour; acids, eg phosphoric, citric, maleic, fumaric or tartaric acids; buffering agents, eg phosphates; sugars, eg fructose, sorbitol or sucrose. The medicament may also contain balanced nutrients such as fats, carbohydrates, proteins, minerals and vitamins. When the medicament is in the form of a dry powder it may also contain an effervescent couple, eg sodium bicarbonate/citric acid.

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When the medicament is in the form of a liquid for oral administration we prefer it to contain from 0.5 to 60.0% w/v, more preferably 0.5 to 30.0% w/v, eg about 6.0% w/v of the dextran.

5 The medicament may be made simply by mixing the ingredients in any convenient order. The mixture may then be filled into suitable containers, eg for dry powder formulations, sachets and for liquid formulations, 100 to 500ml cartons or bottles, which may be pasturised or
10 sterilised depending on the heat stability of the various components.

 The dose to be administered will, of course, vary with the concentration of dextran in the medicament, the mode of administration and the needs of the patient. We
15 prefer the dose of dextran to be administered orally per day to be in the range 10 - 100g, more preferably in the range 25 - 75g per day. We prefer the total daily dose to be administered in 1 - 4 and preferably 2 unit doses. We
20 prefer the unit dose to be in the range 10 - 30g and more preferably to be about 15g.

 We have also found that the dextran can be used advantageously together with other glucose polymers.

 According to a yet further feature of the invention we provide a method of treatment of a patient with hepatic
25 or renal failure which comprises administering an

effective amount of a mixture of a dextran of weight average molecular weight of from 10,000 to 50,000,000 with glucose polymers other than dextran, to such a patient.

We also provide a composition suitable for the
5 treatment of a patient with hepatic or renal failure, which comprises a dextran of weight average molecular weight of from 10,000 to 50,000,000 in admixture with glucose polymers other than dextran.

We further provide a dextran of weight average
10 molecular weight of from 10,000 to 50,000,000 in admixture with glucose polymers other than dextran, for use in the manufacture of a medicament for the treatment of hepatic or renal failure.

The dextran in these mixtures is preferably as
15 described above.

We prefer the glucose polymers other than dextran to be starch hydrolysates, and as such to be mixtures of glucose and polyglucose molecules having a wide range of numbers of glucose units per molecule. We prefer the
20 glucose polymers to contain an average of 2 - 10 and more preferably 4 - 6 glucose units per molecule.

We prefer the ratio of dextran to glucose polymers other than dextran to be in the range 1:0.3 to 3, eg 1:1 by weight.

25 The compositions or medicaments may be suitable for

i.v. or preferably oral administration.

For i.v. administration it is preferred that less than 5% of the total linkages present in the glucose polymers other than dextran are alpha 1,6 linkages.

5 For oral administration the glucose polymers other than dextran may contain a proportion, eg 10% by weight of polymers which have more than 10 glucose units per molecule, and may have present an unspecified number of alpha 1,6 linkages. For oral administration we
10 particularly prefer the glucose polymers other than dextran to comprise 3% glucose, 7% maltose, 5% maltotriose and 85% polyglucose molecules having from 4-15 glucose units per molecule (average number of glucose units = 5). Such glucose polymers are substantially those sold under
15 the Trade Mark CALOREEN.

The glucose polymers other than dextran may be prepared by the enzymatic hydrolysis of starch, substantially as described in British Patent Specification No 1,444,901 or in US Patent Specification No 4,182,756.

20 The compositions and medicaments may be in the form of a syrup, tablet, dry powder, which may be dissolved in a suitable solvent, eg water prior to administration, or a liquid, eg an aqueous solution. The medicament may be incorporated into either a liquid or solid foodstuff, eg
25 bread, biscuits, yoghurt, tea or coffee. The compositions

and medicaments may also contain a pharmaceutically acceptable adjuvant, diluent or carrier. For tablets suitable adjuvants, diluents and carriers are lactose, starch, talc or stearic acid, and for i.v. formulation
5 surfactants and preservatives. The i.v. formulations may be made isotonic with, for example, sodium chloride or phosphate..

The medicaments and compositions according to the invention are particularly suitable for the treatment of
10 one or more of the following; cirrhosis of the liver, especially alcoholic liver cirrhosis, liver cancer, ingestion of toxins, liver disease such as end stage liver disease or viral hepatitis, early stage renal failure, portosystemic encephalopathy or hepatic encephalopathy.

15 Industrial Applicability

In addition to use in the treatment of patients who have defective liver or kidneys or who have had their kidneys removed, the formulations and methods of the invention may be used to remove other toxins from the
20 body. These toxins may have been generated within the body, eg as the result of disease, or may have been assimilated by the body, eg excessive lead or copper. In certain instances the body may have impaired or very slow mechanisms for the removal of these toxins, and in others,
25 eg as with lead, there may be no natural mechanism for its

removal.

The method of treatment according to the invention leads to the alleviation of symptoms experienced by patients suffering from hepatic or renal failure. It may lead to a reduction in the level of nitrogenous waste products by lowering the pH of the colon causing the conversion of ammonia to ammonium ions which may then be excreted in the faeces. Further, the administration of a dextran may lead to an increased colloidal osmotic pressure in the colon, which may facilitate the excretion of urea with the faeces. Both effects should reduce the workload of the kidneys. The administration of dextran should also lead to a decrease in the plasma concentration of waste products such as ammonia, urea, creatinine or phosphate which are typically found in high concentrations in patients suffering from renal failure.

The method of treatment according to the invention is advantageous over the conventional use of lactulose in particular, in that gastrointestinal disturbances such as nausea and flatulence are not found to occur, for example we have found that the administration of dextran orally to humans in 50g doses causes no adverse gastrointestinal effects. Unlike lactulose for which large doses are necessary, small doses of dextran have been found to be effective. Furthermore loss of free water through osmotic

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diarrhoea is not a problem occurring on administration of dextran.

The invention is illustrated but in no way limited by the following Examples.

5 Example 1

When five ileostomy patients, ie patients in which the colon is circumvented by the provision of a tube leading from the ileum to the outside of the body, were given 50g dextran (weight average Molecular Weight 70,000) orally, it was shown that between 70 and 85% of the dextran was recovered intact in the stool. These results showed that the dextran was not being hydrolysed in the small intestine. To demonstrate that dextran is hydrolysed in the large intestine and to investigate its effect on the pH of the colon the following experiments were carried out on six normal volunteers.

Method

Day -1	Sample of normal stool collected.
Day 0	50g of dextran (weight average Molecular Weight 70,000) dissolved in water administered orally to the volunteer with 25 radio-opaque pellets.
Day 0-4	Stool samples were collected on a 24 hour basis.
25	Samples were worked through to provide a

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supernatant by measuring the stool volume and adding an equal volume of distilled water. The suspension was centrifuged and the supernatant filtered.

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The pH and radio-opaque marker count of all the stool samples were determined.

10

The supernatants were analysed by Gel Permeation Chromatography (GPC) for dextran content and for the molecular weight distribution of any hydrolysed dextran.

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ResultsVolunteer 1

	<u>Day</u>	<u>Stool WT(g)</u>	<u>Pellet Recovery</u>	<u>Stool pH</u>
5	-1	310	-	7.10
	0	-	-	-
	1	150	4	6.85
	2	105	10	7.18
	3	498	11	6.32
	4	165	-	6.27

10

Comments

No evidence of dextran by GPC.

No hydrolysed components detected.

Volunteer 2

	<u>Day</u>	<u>Stool WT(g)</u>	<u>Pellet Recovery</u>	<u>Stool pH</u>
15	-1	81	0	6.39
	0	Nil	-	-
	1	197	8	6.77
	2	287	16	6.77
	3	260	1	6.84
20	4	112	0	7.01

Comments

No evidence of dextran by GPC.

No hydrolysed components detected.

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Volunteer 3

	<u>Day</u>	<u>Stool WT(g)</u>	<u>Pellet Recovery</u>	<u>Stool pH</u>
	-1	157	-	6.86
	0	-	-	-
5	1	151.4	19	6.52
	2	229.8	5	6.72
	3	-	-	-
	4	115.6	-	6.88

Comments

- 10 No evidence of dextran by GPC.
No hydrolysed components detected.

Volunteer 4

	<u>Day</u>	<u>Stool WT(g)</u>	<u>Pellet Recovery</u>	<u>Stool pH</u>
	-1	141.0	0	6.71
15	0	169.9	3	6.34
	1	78.3	11	6.61
	2	171.0	9	6.88
	3-4	279.4	2	6.75

Comments

- 20 No abdominal symptoms after administration of dextran.
No evidence of dextran by GPC.
No hydrolysed components detected.

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Volunteer 5

	<u>Day</u>	<u>Stool WT(g)</u>	<u>Marker Recovery</u>	<u>Stool pH</u>
	-1	175	-	6.70
	0	127	5	6.04
5	1	260	20	6.57
	2	0	0	-
	3	135	0	7.02
	4	299	0	6.93

Comments

10 No abdominal symptoms experienced after administration of dextran.

No evidence of dextran by GPC.

No hydrolysed components detected.

Volunteer 6

	<u>Day</u>	<u>Stool WT(g)</u>	<u>Marker Recovery</u>	<u>Stool pH</u>
	-1	-	-	-
	0	102.3	7	5.04
	1	191.2	16	6.67
	2	127.8	1	6.76
20	3	285.2	0	6.10
	4	164.6	0	6.08

Comments

No abdominal symptoms experienced after administration of dextran. No evidence of dextran by GPC.

25 No hydrolysed components detected.

Comments

No intact dextran was recovered, nor any hydrolysed components detected, in any of the stools from the six volunteers, indicating that the dextran administered was being completely hydrolysed and absorbed in the colon.

In four of the volunteers the pH in the colon was significantly reduced.

None of the three volunteers questioned (volunteers 4, 5 and 6) experienced any gastrointestinal disturbances after the administration of dextran.

Example 2Enema Formulations

- a) 7.5% w/v dextran (15g)
200ml distilled water.
- b) 7.5% w/v dextran (15g)
0.9% w/v saline solution
200ml distilled water.

What we claim is:-

1. A dextran of weight average molecular weight in the range 10,000 to 50,000,000 for use in the manufacture of a medicament for the treatment of hepatic or renal failure.
- 5 2. A dextran according to Claim 1 in which the medicament is in a form suitable for rectal administration.
3. A dextran according to Claim 1 in which the medicament is in a form suitable for oral administration.
4. A dextran according to Claim 1 in which the
10 medicament is in the form of a dry powder.
5. A unit dose for the treatment of hepatic or renal failure which comprises 10-30g of a dextran of weight average molecular weight in the range 10,000 to 50,000,000.
6. A dextran according to Claim 1 in admixture with
15 glucose polymers other than dextran.
7. A dextran according to Claim 6 in which the glucose polymers other than dextran contain on average 2 to 10 glucose units.
8. A dextran according to Claim 6 in which the ratio of
20 glucose polymers other than dextran to dextran is in the range 3 to 0.3:1 by weight.
9. A composition suitable for the treatment of hepatic or renal failure which comprises a dextran of weight average molecular weight of from 10,000 to 50,000,000 in
25 admixture with glucose polymers other than dextran.

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10. A formulation suitable for rectal administration which comprises up to 15% w/v of a dextran in aqueous solution.

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 87/00550

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC ⁴ : A 61 K 31/715		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC ⁴	A 61 K C 08 B	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category [*]	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	US, A, 3823233 (CARMELO GIORDANO et al.) 9 July 1984 see the whole document --	1-5
A	EP, A, 0153013 (FISONS) 28 August 1985 --	
A	EP, A, 0076355 (ABBOTT LABORATORIES) 13 April 1983 --	6,7
X	GB, A, 673103 (AKTIEBOLAGET PHARMACIA) 4 June 1952 see page 1, lines 20-35; claims --	1-5
X	Chemical Abstracts, volume 72, no. 25, 22 June 1970, (Columbus, Ohio, US), P.R. MacLean et al.: "Glomerular permeability to high molecular weight dextrans in acute ischemic renal failure and postural proteinuria", see abstract no. 130332g, & Clin. Sci. 1970, 38(1), 93-9 -----	1-5
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>[*] Special categories of cited documents: ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
4th November 1987	30 NOV 1987	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	M. VAN MOL	

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/GB 87/00550 (SA 18138)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 12/11/87

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3823233	03/07/74	None	
EP-A- 0153013	28/08/85	JP-A- 60188403 AU-A- 3819385	25/09/85 08/08/85
EP-A- 0076355	13/04/83	AU-A- 8870482 JP-A- 58069810	14/04/83 26/04/83
GB-A- 673103		None	

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